REVIEW ARTICLE

Anaphylaxis During the Perioperative Period

David L. Hepner, MD*, and Mariana C. Castells, MD, PhD†

*Department of Anesthesiology, Perioperative and Pain Medicine, and †Allergy and Clinical Immunology Training Program, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

Anesthesiologists use a myriad of drugs during the provision of an anesthetic. Many of these drugs have side effects that are dose related, and some lead to severe immune-mediated adverse reactions. Anaphylaxis is the most severe immune-mediated reaction; it generally occurs on reexposure to a specific antigen and requires the release of proinflammatory mediators. Anaphylactoid reactions occur through a direct non-immunoglobulin E-mediated release of mediators from mast cells or from complement activation. Muscle relaxants and latex account for most cases of anaphylaxis during the perioperative period. Symptoms may include all organ systems and present with bronchospasm and cardiovascular collapse in the most severe cases. Management of anaphylaxis includes discontinuation of the presumptive drug (or latex) and anesthetic, aggressive pulmonary and cardiovascular support, and epinephrine. Although a serum tryptase confirms the diagnosis of an anaphylactic reaction, the offending drug can be identified by skin-prick, intradermal testing, or serologic testing. Prevention of recurrences is critical to avoid mortality and morbidity.
(Anesth Analg 2003;97:1381–95)

The term "anaphylaxis" was coined by Nobel prize recipients Portier and Richet (1) in 1902, when they described a dog that had tolerated a previous injection of actinotoxin, a jellyfish toxin, but reacted with bronchial spasm, cardiorespiratory arrest, and death to a smaller dose 14 days later. Whereas prophylaxis in Greek means "protection," anaphylaxis means "opposite protection" or "against protection" (2). Anaphylaxis generally occurs on reexposure to a specific antigen and requires the release of proinflammatory mediators, but it can also occur on first exposure, because there is cross-reactivity among many commercial products and drugs.

Immune-mediated allergic reactions are classified, according to their mechanism, on the basis of the Gell and Coombs classification. Whereas anaphylaxis is a Type I immunoglobulin (Ig)E-mediated hypersensitivity reaction involving mast cells and basophils, contact dermatitis is a Type IV T-lymphocyte cell-mediated delayed-type hypersensitivity reaction. Other immune-mediated reactions include Type II reactions in which IgG, IgM, and complement mediate cytotoxicity and Type III reactions in which immune-complex formation and deposition leads to tissue damage (3). Anaphylactoid reactions occur through a direct nonimmune-mediated release of mediators from mast cells and/or basophils or result from direct complement activation, but they present with clinical symptoms similar to those of anaphylaxis (3,4).

Anaphylaxis is generally an unanticipated severe allergic reaction, often explosive in onset, that can occur perioperatively, especially during a surgical procedure when multiple drugs are administered during the conduction of an anesthetic. Because patients are under drapes and mostly unconscious or sedated, the early cutaneous signs of anaphylaxis are often unrecognized, leaving bronchospasm and cardiovascular collapse as the first recognized signs of anaphylaxis. A survey of anaphylaxis during anesthesia demonstrated that cardiovascular symptoms (73.6%), cutaneous symptoms (69.6%), and bronchospasm (44.2%) were the most common clinical features (5).

The incidence of anaphylaxis and anaphylactoid reactions during anesthesia is very difficult to estimate but has been calculated to range from 1 in 3,500 to 1 in 13,000 cases (6,7). Another report from Australia estimated the incidence to be between 1 in 10,000 and 1 in 20,000 (8), whereas the most recent report, from Norway, estimated the incidence to be 1 in 6,000 (9). Muscle relaxants are associated with the most frequent incidence of anaphylaxis, and over the last two decades, natural rubber latex (NRL, or *cis*-1,4-polyisoprene) has emerged as the second most common cause of anaphylaxis (5,10). However, one report (5) found that the incidence of cases of

Supported by the Department of Anesthesiology, Perioperative and Pain Medicine and by the Department of Medicine, Brigham and Women's Hospital, Harvard Medical School.

Accepted for publication June 6, 2003.

Address correspondence and reprint requests to David L. Hepner, MD, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, 75 Francis St., Boston, MA 02115. Address e-mail to dhepner@partners.org.

DOI: 10.1213/01.ANE.0000082993.84883.7D

0003-2999/03

latex anaphylaxis is decreasing as a result of identification of at-risk patients and preventive measures. Antibiotics and anesthesia induction drugs account for the next group of drugs more likely to lead to an anaphylactic reaction (5,10). Table 1 outlines the common drugs involved in perioperative anaphylaxis in France (5).

Serious problems are unusual during surgery (0.4% of cases), but anesthesia contributes to a third of these cases (9). Allergic reactions are among the major factors that contribute to morbidity and mortality during an anesthetic and to changes in postoperative care (9). A recent review of serious intraoperative problems highlighted a case of fatal anaphylactic shock and suggested that preventive strategies are needed for anaphylaxis (9). Because anaphylaxis is a rare event that is not the first consideration for the anesthesiologist, its management in a full-scale anesthesia simulator has been suggested (11). In one study, none of 42 anesthesiologists tested on a simulator made the correct diagnosis during the first 10 min of anaphylaxis, and most of them failed to have a structured plan for its treatment (11).

Earlier review articles focused on the definition, diagnosis, and management of anaphylaxis (12,13). Other review articles highlight drugs involved in anaphylactic and anaphylactoid reactions but concentrate only on the most common causative drugs (14). Even recent reviews on anaphylaxis during anesthesia devote a limited portion to drugs likely to induce anaphylaxis (15). This review will identify most drugs implicated in anaphylaxis and will discuss its diagnosis and management. A MEDLINE literature search with the key words "anesthesia" plus "anaphylaxis" or "hypersensitivity" or "allergy" produced 491 articles from 1966 until October 2002. These articles were reviewed, and the common drugs associated with perioperative anaphylaxis were identified. Then a search of each specific drug and the key words "anaphylaxis," "hypersensitivity," or "allergy" was conducted. In addition, the references of relevant articles were reviewed to identify other articles missed in the original search. Finally, additional references were identified from the book *Drug Allergy* (16) and from the most recent survey of anaphylaxis during anesthesia (5).

Pathophysiology

Anaphylaxis is a clinical syndrome that affects multiple organ systems. The clinical manifestations of anaphylaxis are derived from the acute release of mediators from mast cells and possible basophils. On initial exposure to an antigen in susceptible individuals, IgE is produced and binds to mast cells and basophils. On reexposure, the multimeric antigen cross-links two IgE receptors, inducing the tyrosine phosphorylation of their cytoplasmic immune tyrosine activation motifs by Lyn and Syk tyrosine kinases. This initiates a signal-transduction cascade, which culminates in the increase of intracellular calcium and the release of preformed mediators such as histamine, proteases (tryptases), proteoglycans, and platelet-activating factor (3,17). Phospholipid metabolism then leads to the generation of potent inflammatory leukotrienes (LTC_4, LTE_4, and LTD_4) and prostaglandins (PGD_2). Histamine, PGD_2, and LTC_4 are potent vasoactive mediators implicated in vascular permeability changes, flushing, urticaria, angioedema, hypotension, and bronchoconstriction (Fig. 1).

Histamine receptors are present in the skin, gastrointestinal tract, heart, vascular bed, and bronchial smooth muscle. Whereas histamine 1 receptors are responsible for increases in mucous production, heart rate, and flushing, histamine 2 receptors lead to an increase in vascular permeability, gastric acid secretion, and airway mucus production. PGD_2 and LTC_4 receptors are present in the skin, bronchial smooth muscle, and vascular bed and cause bronchoconstriction, a wheal and flare response, and increased vascular permeability. Proteases prevent local coagulation and degrade bronchodilating peptides. Heparin and platelet-activating factor can produce local and systemic anticoagulation.

Anaphylactoid reactions are derived from the activation of the complement and/or bradykinin cascade and the direct activation of mast cells and/or basophils (Fig. 1). Clinical manifestations of anaphylactoid reactions are indistinguishable from anaphylactic reactions. These reactions are rapid in onset and start within seconds to minutes of exposure to the allergen. Symptoms progress rapidly and can affect most organ systems, including the skin (pruritus, flushing, urticaria, and angioedema) and eyes (conjunctivitis), the upper (rhinitis and angioedema) and lower (bronchoconstriction with wheezing and dyspnea, and cyanosis) airway, the intestinal tract (abdominal pain, nausea, vomiting, and diarrhea), and the cardiovascular system (tachycardia, hypotension, and shock), and can lead to cardiovascular collapse and death (4) (Table 2). The onset and type of symptoms depend on the allergen concentration, although minute amounts of allergen have been shown to produce severe and even fatal reactions. The patient's sensitivity and the route of administration are determining factors, and IV infusion of allergen can trigger rapid cardiovascular symptoms.

Diagnosis

Whereas the initial diagnosis of perioperative anaphylaxis relies on the history and physical examination, the retrospective diagnosis is based on serologic and

Table 1. Drugs Involved in Perioperative Anaphylaxis (5)

Substance	Incidence of perioperative anaphylaxis (%)	Most commonly associated with perioperative anaphylaxis
Muscle relaxants	69.2	Succinylcholine, rocuronium, atracurium
Natural rubber latex	12.1	Latex gloves, tourniquets, Foley catheters
Antibiotics	8	Penicillin and other β-lactams
Hypnotics	3.7	Propofol, thiopental
Colloids	2.7	Dextran, gelatin
Opioids	1.4	Morphine, meperidine
Other substances	2.9	Propacetamol, aprotinin, chymopapain, protamine, bupivacaine

skin tests (Fig. 2). Serum tryptase is a mast cell protease that is increased in cases of anaphylaxis, signaling an immune-mediated mechanism. An increase in human α and β tryptase, the predominant mast cell proteases, can be measured in serum and plasma 30 min after the first signs of anaphylaxis and correlate with the presence of hypotension. Tryptase's half-life is 2 h, and the levels gradually decrease over time. Tryptase may not be increased in the absence of hypotension (18,19), or it may remain increased for days in cases of late-onset, biphasic, and protracted anaphylaxis (20,21). Mast cell tryptase can also be released by pharmacologic drugs that cause direct nonimmunologic mast cell activation (22). An increase of serum tryptase does not differentiate an anaphylactic from an anaphylactoid reaction (23). Similarly, an absence of serum tryptase does not eliminate an anaphylactic reaction, because there have been reports of anaphylaxis with positive tests for IgE antibodies in the setting of an absence of serum tryptase. In conclusion, although serum tryptase is a helpful indicator of an anaphylactic reaction, it does not differentiate an anaphylactic from an anaphylactoid reaction. Histamine in serum is not measured routinely because of its half-life of only a few minutes (20,24). Collections of urine histamine for 24 h after the anaphylactic episode will reflect the release from mast cells and basophils (20,24).

In vitro tests available in clinical practice detect the presence of IgE antibodies by the radioallergosorbent test (RAST, Pharmacia CAP system). This test measures the presence of specific IgE antibodies in serum that bind to a disk coupled with the specific drug and can be performed if the patient has extensive skin lesions, is receiving drugs such as antihistamines, or has presented with a recent episode of anaphylaxis. RAST tests are highly specific, but the sensitivity is low for most drugs. Subjects may remain sensitized for up to 30 yr after exposure to muscle relaxants, unlike other drugs, such as β-lactam antibiotics, for which individuals lose sensitization over time (6,16). Basophil histamine release is a research assay not commercially available in the United States and not approved by the US Food and Drug Administration (FDA). It is performed *in vitro* by exposing the patient's basophils to the drug suspected of inducing anaphylaxis (25). It can be used for the detection of IgE reactions to muscle relaxants and propofol.

In vivo testing includes skin testing, which is performed by prick and intradermal techniques. Routine skin testing of all patients undergoing anesthesia in the absence of prior adverse reactions to anesthetic drugs is not recommended because of the presence of subclinical IgE sensitization (26,27). In the general population, 9.3% have a positive skinprick test to one or more muscle relaxants, and specific IgE to quaternary ammonium ions is found in the absence of clinical symptoms (26). Superficial dermal mast cells are triggered by the prick technique, and nonspecific irritation is its major limitation. A positive test has a high predictive value in the setting of a history of anaphylaxis. Prick tests are usually negative with local anesthetics, and in the setting of a positive clinical history, there is the need for an evaluation with a graded challenge (28). Intradermal skin testing is performed by diluting the concentration of the prick test by 1:10 and is used for local anesthetics, muscle relaxants, and propofol. At least 0.2–0.3 mL is introduced intradermally, eliciting a response from a deeper mast cell population. The risk of anaphylaxis induced by skin testing is small (<0.1% for antibiotics). Skin testing should be done 4–6 wk after the anaphylactic episode because of mast cell and basophil-mediator depletion. Because of the risk of inducing a systemic reaction, skin tests should be performed only by trained physicians in a setting with adequate resuscitative equipment.

Management of Perioperative Anaphylaxis

The management of anaphylaxis consists of withdrawing the offending drug, interrupting the effects of the preformed mediators that were released in response to the antigen, and preventing more mediator release (Fig. 3). Management must be immediate, because anaphylaxis is life threatening and may produce cardiovascular collapse (Table 3). Immediate discontinuation of the anesthetic and of drugs and early

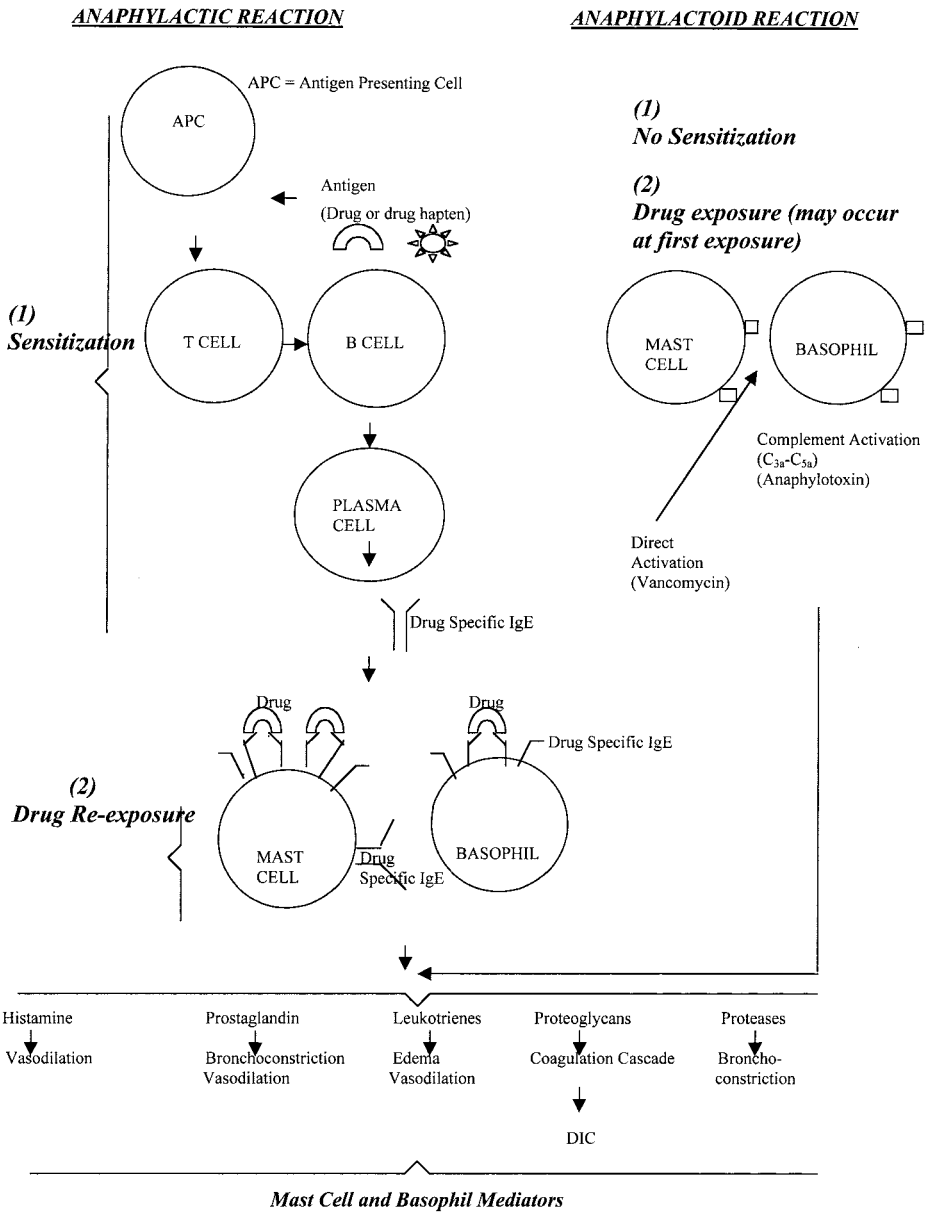

Figure 1. Anaphylactic and anaphylactoid reactions. Anaphylaxis is a clinical syndrome that affects multiple organ systems and occurs after the sudden release of chemical mediators from tissue mast cells or circulating basophils mediated by the cross-linking of immunoglobulin E (IgE) antibodies. Anaphylactoid reactions are clinically indistinguishable from anaphylactic reactions but occur through a direct non-IgE-mediated release from mediators of mast cells or from complement activation. DIC = disseminated intravascular coagulation.

administration of epinephrine are the cornerstones of treatment. Epinephrine is the drug of choice in the treatment of anaphylaxis, because its α_1 effects help to support the blood pressure while its β_2 effects provide bronchial smooth-muscle relaxation. Epinephrine is used at 5- to 10-μg IV bolus (0.2 μg/kg) doses for hypotension and at 0.1- to 0.5-mg IV doses in the presence of cardiovascular collapse (2). Failure to recognize anaphylaxis and treat it promptly with epinephrine may result in biphasic or protracted anaphylaxis or in a fatal outcome (29,30).

Airway support with 100% oxygen will increase oxygen delivery and compensate for the increased oxygen consumption. IV crystalloid (2–4 L) replacement will compensate for the peripheral vasodilation that often accompanies anaphylaxis. Histamine 1 blockers (e.g., diphenhydramine 0.5–1 mg/kg), histamine 2 blockers (e.g., ranitidine 150 mg or cimetidine 400-mg IV bolus), bronchodilators (e.g., albuterol and ipratropium bromide nebulizers), and corticosteroids (e.g., hydrocortisone 1–5 mg/kg) should be given (2,31,32). Histamine 1 blockers are used in the early phases of anaphylaxis, but once cardiovascular collapse occurs, their role is controversial (33). Corticosteroids can decrease the airway swelling and prevent recurrence of symptoms, as seen in biphasic or protracted anaphylaxis (31). Hydrocortisone is the preferred steroid because it has a fast onset. Extubation should be delayed, because airway swelling and inflammation may continue for 24 h (2). An epinephrine infusion may be necessary to maintain the blood pressure, and bronchodilators should be continued during

Table 2. Clinical Manifestations of Anaphylaxis (4)

Organ system	Signs and symptoms	Signs during anesthesia
Cutaneous	Flushing, pruritus, urticaria, angioedema	Flushing,[a] urticaria, angioedema
Gastrointestinal	Nausea and vomiting, abdominal cramping, diarrhea	Absent or difficult to appreciate in patients receiving general anesthesia. May be present in patients under regional anesthesia or monitored anesthesia care
Respiratory	Rhinitis, laryngeal edema, shortness of breath, wheezing, respiratory arrest	Increased peak inspiratory pressure, increased end-tidal carbon dioxide, decreased oxygen saturation, wheezing, bronchospasm
Cardiovascular	Tachycardia, hypotension, cardiac arrhythmias, cardiovascular collapse	Tachycardia, hypotension, cardiac arrhythmias, cardiac arrest
Renal	Decreased urine output	Decreased urine output secondary to acute tubular necrosis
Hematologic	DIC	DIC

DIC = disseminated intravascular coagulation.
[a] The skin is often covered, and it may be difficult to appreciate any cutaneous manifestations.

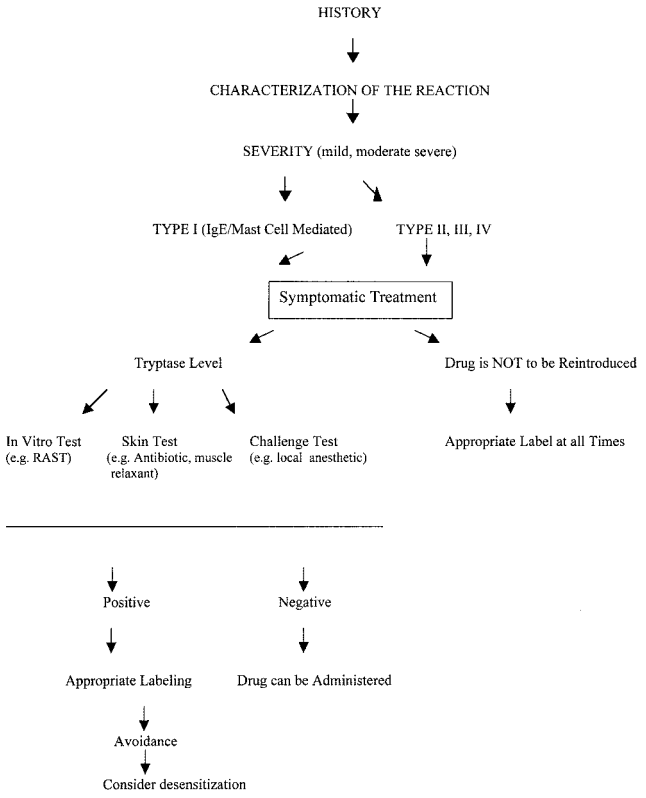

Figure 2. Simple algorithm for the diagnosis of perioperative anaphylaxis. The initial diagnosis of perioperative anaphylaxis relies on the history and physical examination. Whereas *in vitro* tests are used to confirm the diagnosis (serum tryptase) and to identify the offending drug or substance (radioallergosorbent test; RAST), *in vivo* tests (e.g., skin test) are used to identify the offending drug or substance with more sensitivity and specificity. IgE = immunoglobulin E.

bronchospasm. Histamine 1 receptor antagonists should be continued in the presence of urticaria and angioedema, and a histamine 2 receptor antagonist should be added to a histamine 1 receptor antagonist in the setting of hypotension.

Preliminary work has demonstrated that the histamine 3 receptor is also involved in anaphylaxis (34). These receptors have been identified on presynaptic terminals of the sympathetic nervous system that innervates the heart and systemic vasculature, and they inhibit endogenous epinephrine release from the sympathetic nerves (35). Histamine 3 receptor blockade has been shown to improve left ventricular systolic function and heart rate in canine anaphylaxis when compared with controls (34).

Prevention of Perioperative Anaphylaxis

A careful history regarding adverse drug reactions and allergies should be conducted before any surgical procedures requiring anesthesia. Identification of at-risk patients will lead to avoidance of a particular drug and is likely to prevent anaphylaxis. Atopic individuals with increased IgE are at risk for allergic reactions to propofol and latex (36,37). Health-care workers and patients with multiple prior surgical procedures can be sensitized to latex and may develop anaphylaxis when exposed to latex (37). Females are more likely than males to have anaphylaxis during anesthesia, with a 3:1 ratio (5). Avoidance of drugs that produced anaphylaxis and positive tests during a prior anesthetic has been demonstrated to prevent an episode of anaphylaxis from recurring (38,39).

There is little benefit in premedicating allergic patients with histamine 1 and histamine 2 blockers or corticosteroids before surgery or anesthesia (40,41). Although they could minimize the severity of anaphylaxis, these drugs may also blunt the early signs of anaphylaxis, leaving a full-blown episode as the presenting sign. These drugs should be reserved for the early treatment of anaphylaxis.

Patients with anaphylaxis who have no alternative drug available can be desensitized (42–47). Eligible

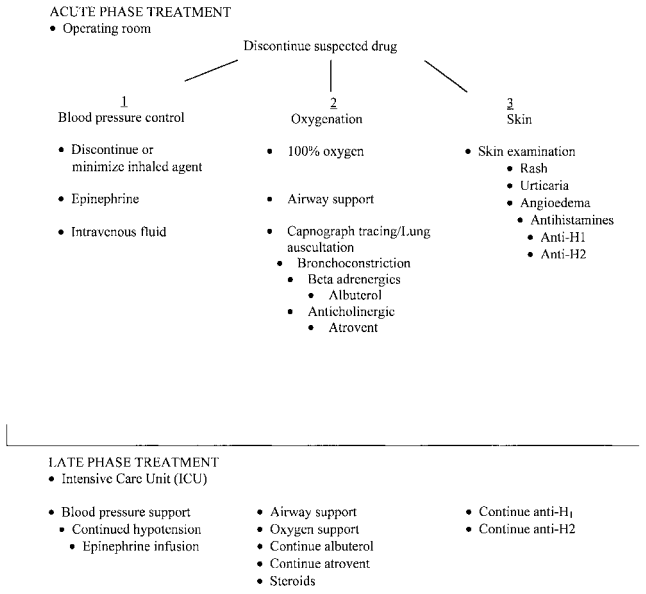

Figure 3. Step-by-step approach to the management of perioperative anaphylaxis. Treatment of the acute phase of perioperative anaphylaxis relies on blood pressure maintenance and airway support. Treatment of the late phase of perioperative anaphylaxis relies on drug support measures, including histamine 1 (H1) and histamine 2 (H2) blockers and corticosteroids.

patients have an IgE mechanism with mast cell activation and mediator release (46). The desensitization mechanism allows for the incremental introduction of the specific drug to the targeted doses. Patients transiently lose the skin-test positivity after desensitization. There is temporary tolerance as long as there are continued systemic levels of the allergen. The mechanism is unknown, but signal transduction in mast cells is abolished during the process (47).

Specific Drugs

Local Anesthetics

Local anesthetics belong to the amide or ester groups. Ester local anesthetics, such as procaine, chloroprocaine, tetracaine, and benzocaine, have a lipophilic or aromatic group, an intermediate ester linkage, and a hydrophilic quaternary amine side chain. Amide local anesthetics, such as lidocaine, mepivacaine, prilocaine, bupivacaine, levobupivacaine, and ropivacaine, differ in that they have an intermediate amide linkage. The metabolism of amide local anesthetics is primarily in the liver, whereas that of esters is via plasma cholinesterases to paraaminobenzoic acid.

Anaphylactic reactions to amide local anesthetics are extremely rare, and true allergic reactions to esters account for <1% of all drug reactions to local anesthetics (28,48,49). True Type I IgE-mediated allergic reactions are usually due to the paraaminobenzoic acid metabolite from esters or methylparaben (a preservative). Epinephrine and metabisulfite, often present in local anesthetics, can also cause adverse drug reactions. Vasovagal responses, tachycardia, lightheadedness, metallic taste, and perioral numbness can result from intravascular injection of the local anesthetic, epinephrine, or both (28). The most common immune-mediated reaction to local anesthetics is a delayed hypersensitivity reaction (Type IV reaction), or contact dermatitis (49).

Skin and challenge tests are used for diagnosis, and it is important to use preservative-free local anesthetics. There is no cross-reactivity between amide and ester local anesthetics, except in cases in which a preservative is the allergen. Although cross-reactivity occurs among esters, it is very unusual among amides.

Muscle Relaxants

Muscle relaxants are the most common cause of anaphylaxis during anesthesia. Whereas the overall incidence is 1 in 6500 patients undergoing anesthesia with a muscle relaxant (7), muscle relaxants account for 69.2% of anaphylactic reactions during an anesthetic (5). IgE antibodies to the two quaternary or tertiary ammonium ions mediate anaphylaxis. Succinylcholine contains a flexible molecule that can cross-link two mast cell IgE receptors and, thus, induce mast cell degranulation. Succinylcholine is more likely to cause anaphylaxis than nondepolarizing muscle relaxants with a rigid backbone between their two ammonium ions (e.g., pancuronium or vecuronium) (6). The incidence of anaphylaxis is also more frequent with benzylisoquinolinium compounds than with aminosteroid compounds. Many over-the-counter drugs, cosmetics, and food products contain quaternary or tertiary ammonium ions that could sensitize people (50). Therefore, anaphylaxis may develop on the first exposure to a muscle relaxant in a sensitized patient. Cross-sensitivity between muscle relaxants occurs in up to 60% of patients (50–52). Furthermore, neostigmine and morphine also contain ammonium ions that may cross-react with muscle relaxants.

Another mechanism involved in adverse reactions to muscle relaxants, independent of and more common than IgE-mediated reactions, is direct mast cell degranulation that causes the release of histamine and other mediators (17). This histamine release is not immune mediated and does not require prior exposure. Benzylisoquinolinium compounds, such as D-tubocurarine, metocurine, doxacurium, atracurium, and mivacurium, are more likely to cause direct mast cell degranulation than aminosteroid compounds such as pancuronium, vecuronium, rocuronium, and

Table 3. Treatment of Perioperative Anaphylaxis

Management[a]	Action
Discontinuation of anesthetic or drug	Decreased vasodilation, decreased antigen delivery
100% Oxygen airway support	Increase oxygen delivery, maintain airway
IV fluids	Compensate for systemic vasodilation
Epinephrine	
5–10-μg initial bolus up to 100–500 μg for vascular collapse	$Alpha_1$ agonist
Start drip with 1 μg/min for refractory hypotension	$Beta_2$ agonist
Diphenhydramine 25–50 mg	H1 receptor blocker (antihistamine)
Ranitidine 150-mg bolus or cimetidine 400-mg bolus	H2 receptor blocker
Albuterol 0.3% and ipratropium bromide 0.03% nebulization	Bronchial smooth-muscle relaxation
Corticosteroids	
0.5–1.0 mg/kg methylprednisolone	Prevent late and delayed symptoms
1–5 mg/kg hydrocortisone	

H1 = histamine 1; H2 = histamine 2.
[a] All doses are given for IV administration.

pipecuronium. Cisatracurium, a benzylisoquinolinium compound and an isomer of atracurium, and succinylcholine have the lowest potency of direct mast cell activation (17,53,54).

Current controversy revolves around the potential for an increased incidence of anaphylaxis to rocuronium when compared with other muscle relaxants (7,55–57). The increased number of allergic reactions to rocuronium in Norway—55 reactions and 3 deaths over 4 yr—led to a "dear doctor letter" from the Norwegian Medicines Agency that recommended rocuronium's withdrawal from routine practice and its use reserved for urgent intubations (57). There is a discrepancy between the reported incidence of anaphylaxis due to rocuronium in Norway (1 in 3,500 anesthetics) and the incidence noted in the United States (1 in 445,000 anesthetics; 80% of worldwide use) (57). This discrepancy has been attributed to multiple factors, including false-positive testing, increased use of the drug, statistical challenge, and, possibly, population genotype differences (58–60). Rocuronium may cause a wheal and flare response independent of mast cell degranulation. Levy et al. (58) demonstrated that intradermal skin testing with rocuronium at concentrations larger than 10^{-4} M (609.70 g/L = 1 M) produced a positive wheal or flare response in 29 of 30 volunteers in the absence of mast cell degranulation. These authors suggest that skin testing with concentrations larger than 10^{-4} M may account for some of the reported cases of rocuronium allergy reported in Europe (58). A report from Australia, using a 1:1000 dilution for intradermal skin testing, demonstrated that rocuronium is intermediate in its potential to cause anaphylaxis (59). This study also demonstrated that the increased incidence of anaphylaxis due to rocuronium in Australia is a result of its increased use (59). Statistical challenges, such as small sample size and biased reporting of newer drugs, may account for the increased incidence of rocuronium anaphylaxis (60).

Routine testing of muscle relaxants is not recommended because of a small positive predictive value (26,27). However, testing is recommended in patients with a history of anaphylaxis to muscle relaxants, and in these cases, intradermal skin tests and prick tests with undiluted muscle relaxants have a high predictive value (16). Skin testing with rocuronium should be performed at concentrations $<10^{-4}$ M, whereas cisatracurium testing should be performed at concentrations $<10^{-5}$ M (929.2 g/L = 1 M) (58). Cross-reactivity between muscle relaxants can be assessed by nonirritant intradermal titration. IgE radioimmunoassay (RIA) can be helpful, especially when intradermal tests are negative in the presence of a positive history of an allergic reaction to a muscle relaxant (61,62). The sensitivity of IgE RIA has been improved by coupling an analog of choline to a polymer (Sepharose) via an ether linkage (63). The morphine radioimmunoassay (RIA) has been found to be more sensitive than muscle-relaxant RIA for the detection of IgE antibodies to muscle relaxants (64).

Opioids

Anaphylactic reactions to opioids are rare. Morphine is a tertiary amine that causes nonimmunological histamine release, and meperidine causes nonimmunological histamine release more often than any other opioid (16). There are reported cases of IgE-mediated reactions to these opioids (6,65,66). Fentanyl belongs to the phenylpiperidine group and does not cause nonimmunological histamine release (16), but there are a few reported cases of IgE-mediated anaphylaxis to fentanyl (67). There is cross-reactivity between different opioids of the same family, but not between phenylpiperidine derivatives (6,16).

IgE antibodies (IgE RIA or RAST) to morphine and meperidine have been detected, and skin tests

have been reported to be positive (6,65,66). However, morphine and meperidine cause histamine release when applied to the skin and may confound the results of positive skin tests. The few cases of anaphylaxis that have been reported with fentanyl have been confirmed with intradermal skin testing (67).

Induction Drugs

Barbiturates. The incidence of anaphylaxis to thiopental is estimated to be 1 in 30,000 administrations, and previous exposure and female sex are associated with an increased incidence (68). Although IgE-mediated hypersensitivity reactions to thiopental, a thiobarbiturate, have been described, no reports of IgE-mediated hypersensitivity reactions to methohexital, an oxybarbiturate, have been described (16). Diagnosis is via the detection of thiopentone-reactive IgE antibodies by the RAST method (6,69,70). Alternative diagnosis is via skinprick or intradermal tests to thiopental with a dilution of 1:1000 to 1:10 of 2.5% thiopental (16).

Propofol. Propofol was originally formulated with the surfactant Cremophor EL, but a series of hypersensitivity reactions prompted a change in the formulation (36,71,72). Propofol (2,6-diisopropylphenol) is currently formulated in a lipid vehicle containing soybean oil, egg lecithin, and glycerol. The incidence of anaphylactic reactions with the new formulation is 1 in 60,000, although it has been reported to cause 1.2% of cases of perioperative anaphylaxis in France (73). A more recent report from the same group in France demonstrated that 2.1% of cases of intraoperative anaphylaxis are due to propofol (5). In a report of 14 patients with documented propofol allergy on first exposure, the 2 isopropyl groups of the propofol were thought to be the sensitizing epitopes (36). Isopropyl groups are present in dermatologic products and may account for anaphylactic reaction to propofol on the first exposure. In addition, there is a report of an anaphylactic reaction to propofol at the time of the third exposure to the drug (72). Phenol may have acted as an antigen and produced sensitization that led to an episode of anaphylaxis on reexposure. Most cases of drug allergy to propofol are IgE mediated, and specific IgE RIA and intradermal skin tests have been reported (36).

Propofol is formulated in a lipid emulsion containing 10% soybean oil, 2.25% glycerol, and 1.2% egg lecithin. The egg lecithin component of propofol's lipid vehicle is a highly purified egg yolk component (74). Ovalbumin, the principal protein of eggs, is present in the egg white. Skinprick and intradermal testing with propofol and with its lipid vehicle (Intralipid) were negative in 25 patients with documented egg allergy (74). The measles-mumps-rubella vaccine does contain small amounts of egg-related antigens (ovalbumin), which are grown in cultures of chick-embryo fibroblasts. However, the measles-mumps-rubella vaccine has been given to egg-allergic children without any episodes of anaphylaxis (75). Therefore, current evidence suggests that egg-allergic patients are not more likely to develop anaphylaxis when exposed to propofol.

Etomidate and Ketamine. Allergic reactions to these two drugs are exceedingly rare (5,16). The most recent review of anaphylaxis during anesthesia did not include any cases related to these two drugs. Etomidate is perhaps one of the most immunologically safe anesthetics (76). Although there is a report of an anaphylactoid reaction with etomidate (77), no *in vivo* or *in vitro* diagnostic method is currently available (16). There are reports of IgE-mediated reactions to ketamine (78,79), and an intradermal skin test has been used in one patient (78).

Benzodiazepines. Allergic reactions to benzodiazepines are extremely rare. The Cremophor EL solvent was responsible for most reactions to benzodiazepines (80). Diazepam is more likely than midazolam to cause an anaphylactic reaction because of the propylene glycol solvent that replaced Cremophor EL. The active metabolite desmethyldiazepam may be responsible for the cross-reactivity with other benzodiazepines (16). Midazolam is a safe drug, because it does not have any active metabolites. Although anaphylactoid reactions to midazolam have been reported, no serologic or cutaneous testing was performed (81). In addition, midazolam has been used safely for the induction of anesthesia in patients with drug allergy (82,83). Cutaneous testing to benzodiazepines has been negative, and no serologic tests are clinically available.

Inhaled Anesthetics

There are no reports of anaphylaxis related to volatile anesthetics. However, these drugs have been associated with hepatic injury due to an immune-mediated toxicity (84). Patients generate an antibody response (IgG antibodies) toward a covalently bound metabolite (trifluoroacetyl metabolite) of halothane, as detected by an enzyme-linked immunosorbent assay (ELISA) (85), and can present with a rash, fever, arthralgia, eosinophilia, and increased liver enzymes (86). Prior administration of halothane increases the incidence and severity of hepatitis. Although volatile anesthetic immune-induced hepatitis is much more common with halothane, other volatile anesthetics with trifluoroacetyl metabolites can induce immune hepatitis (87). Enflurane and isoflurane have been associated with an immune-mediated hepatic injury without prior exposure to halothane (84,88). Two reports support desflurane-induced hepatotoxicity

(89,90), but because of its decreased metabolism, desflurane is less likely to cause immune-mediated hepatitis. Sevoflurane is not metabolized to trifluoroacetyl metabolites and does not cause immune-mediated hepatitis.

Drugs Affecting Coagulation

Aprotinin. Aprotinin is a naturally occurring polybasic polypeptide serine protease inhibitor used in cardiac surgical procedures to decrease blood loss and blood transfusions. Aprotinin is derived from bovine lung and is antigenic in humans. The incidence of allergic reactions to aprotinin given for cardiac surgery is 0.5% but may be as frequent as 2.5%–2.8% on repeat exposure (16,91,92). The risk of an allergic reaction on repeat exposure is increased when it occurs within 6 mo of the last aprotinin use. However, IgG and IgE antibodies take 10–14 days to form, and, therefore, reexposure to aprotinin in the first 24–36 h is less likely to lead to an adverse reaction (91,92). IgE and IgG antibodies have been demonstrated in patients exposed to aprotinin for the first time and are necessary for developing an anaphylactic reaction, but they lack specificity for predictive purposes (91). IgE antibodies are detected with RAST, whereas IgG antibodies are detected with ELISA (91,93). Although there are a few positive cases of cutaneous testing with aprotinin prick or intradermal tests after an allergic reaction, one study demonstrated that a preoperative aprotinin prick test was not predictive of an adverse reaction (91).

Heparin. Heparin is a strongly acidic, anionic, sulfated mucopolysaccharide, and it has a large molecular weight. It is derived from bovine or porcine lung or intestine and is antigenic in humans. Type I IgE-mediated hypersensitivity reactions to heparin are exceedingly rare, and skin tests are used for their diagnosis (94). Although there are no reported cases of anaphylaxis to low-molecular-weight heparin, low-molecular-weight heparin has *in vitro* and *in vivo* cross-reactivity with unfractionated heparin (16). Cross-reactivity has been demonstrated with delayed-type hypersensitivity reactions after performing patch, intradermal, and subcutaneous tests to unfractionated and low-molecular-weight heparin (95,96). The most common reaction to heparin is heparin-induced thrombocytopenia (HIT), a nonanaphylactic reaction mediated via IgG and IgM antibodies, and it occurs in up to 5% of patients receiving heparin for >5 days (16). HIT is less common with low-molecular-weight heparin, but there is also cross-reactivity with unfractionated heparin. Heparin-coated catheters and heparin in arterial and central venous catheters are best avoided in patients with a history of HIT or heparin-induced anaphylaxis.

Protamine. Protamine sulfate is a strongly alkaline, polycationic, small molecule extracted from salmon sperm and used to reverse the anticoagulant effects of heparin. Exposed patients (0.4%–0.76%) can develop an allergic reaction to protamine, and the risk is increased in patients previously exposed to protamine (97,98). Some forms of insulin, such as neutral protamine hagedorn and protamine-zinc insulin, contain protamine, and there is an increased risk for a protamine reaction in diabetic patients exposed to neutral protamine hagedorn and protamine-zinc insulin (99). There is a theoretical risk that patients allergic to fish or those who are infertile or vasectomized are more likely to develop an allergic reaction to protamine (100), because protamine is extracted from salmon sperm. Whereas earlier reports suggest that autoantibodies to sperm may develop after it is reabsorbed in infertile or vasectomized men (101,102), more recent reports have failed to demonstrate an association between protamine allergy and vasectomy, infertility, or fish allergy (16,103). Others have demonstrated the presence of protamine-specific IgG antibody in 29% of vasectomized men and the absence of these antibodies in control patients (104). However, although the presence of these antibodies is more common in patients who have a protamine reaction, it does not imply a cause-and-effect relationship (105).

IgE- and IgG-mediated hypersensitivity, complement activation, nonimmunologic histamine release, and augmentation of thromboxane leading to an increase of the pulmonary artery pressure have been documented (99,106,107). Reactions to protamine include urticaria and systemic hypotension with pulmonary vasoconstriction. Protamine can cause a nonimmunologic dose-related decrease in blood pressure, which is worse when the drug is given rapidly. Cutaneous testing will identify IgE-mediated sensitivity (99). Protamine-specific IgE and IgG antibodies can be measured by solid-phase immunoassay, ELISA, and RAST.

Antibiotics

Penicillin, Cephalosporins, and Other β-Lactam Antibiotics. These are the most commonly used antibiotics during the perioperative period and perhaps some of the most commonly used drugs overall. Penicillin is the most common cause of anaphylaxis in the general population and may account for as many as 75% of anaphylactic deaths in the United States (108). Although most allergic reactions to penicillin occur in patients with a history of a prior reaction to penicillin, one review of the literature found that only 10%–20% of patients who report a penicillin allergy have a documented allergy (109). Most patients usually refer to side effects such as gastrointestinal symptoms or do

not remember exactly why they are "allergic" to penicillin. They may remember that a health-care provider or family member told them not to take penicillin or that someone in their family had a reaction when they received penicillin. Taking a detailed history of the reaction to penicillin will remove most of the questionable cases.

Type I IgE-mediated sensitivity is the most common mechanism in patients with a documented anaphylactic episode or allergy workup. Diagnosis is performed with prick and intradermal skin testing by using minor and major determinants. It has been recommended to skin-test those patients with clinical symptoms consistent with a Type I IgE-mediated reaction (109). The predictive value of a negative penicillin test is 97% because only 3% of patients with a negative skin test who are given penicillin will develop a limited skin rash. Serologic testing with RAST and ELISA do not detect IgE antibodies to minor determinants (16,108). Although Pharmacia has recently introduced a test for specific IgE against penicillin minor determinants in their UniCap system, it is not available in the United States (110,111). Cephalosporin skin testing is available in Europe but not in the United States. Cutaneous testing to cephalosporins indicates that, in some patients, side-specific chain IgE can develop in the absence of penicillin allergy (112).

Some allergy books still quote an 8%–10% risk of cross sensitivity between penicillins and cephalosporins and attribute it to the β-lactam ring that is shared by both (16). However, most of the reported reactions of cross-sensitivity consist of rashes that are not immunologic in origin. In addition, earlier generations of cephalosporins contained trace amounts of penicillin, and this may account for some of the adverse reactions (113). A review of this subject found that patients with an allergy to penicillin were more likely (threefold) to experience an anaphylactic reaction to any other drug (113). Although some experts state that it is safe to administer cephalosporins to penicillin-allergic patients and that penicillin skin tests are not indicated (113), others have recommended avoidance of cephalosporins in those with positive penicillin skin tests or anaphylaxis (109,114,115). Goodman et al. (115) performed a retrospective chart review of intraoperative anesthesia records over a 14-mo period and demonstrated that cephalosporins can be given to patients who claim to be allergic to penicillin. However, a limitation of this study is that patients who reported anaphylaxis to penicillin were excluded.

Vancomycin. Vancomycin is a complex tricyclic glycopeptide and is often the antibiotic used in cases of penicillin resistance or allergy. The classic "red man syndrome" consists of flushing, pruritus with an erythematous rash, and hypotension and occurs in 5%–14% of adults. It usually occurs during rapid vancomycin injection, is due to nonimmunologic histamine release, and accounts for most reactions (116). Management of the red man syndrome includes the use of antihistamines, a slow infusion rate, and division of the total dose. Although it is extremely rare, there are reported cases of IgE-mediated hypersensitivity reactions to vancomycin (16,117). Skinprick tests are usually negative, and there are a few reported positive intradermal skin tests (16). There is a report of successful desensitization after an episode of anaphylaxis (117).

Bacitracin. Bacitracin is a polypeptide complex antibiotic that is used topically or as an irrigation solution. Although contact dermatitis is the most common reaction to this drug, there are reports of intraoperative anaphylaxis due to bacitracin irrigation of surgical sites (118,119). A Type I IgE-mediated reaction is diagnosed by skinprick tests.

Others. Other antibiotics that are often used in the operating room and that may rarely trigger an anaphylactic reaction include clindamycin, gentamicin, and metronidazole. Clindamycin is used against Gram-positive and anaerobic bacteria and usually causes a contact dermatitis. No specific IgE antibody has been found, and skinprick and intradermal skin tests are negative (16). Gentamicin is a broad-spectrum aminoglycoside often used in patients at risk for endocarditis, whereas metronidazole is a nitroimidazole derivative used against anaerobic infections. IgE-mediated hypersensitivity, although previously reported, is extremely rare in both cases (16).

Other Potential Antigens

Povidone-Iodine. Povidone-iodine (betadine) is the most common topical antiseptic solution used in the United States, and there are only a few reports in the literature of anaphylaxis to this drug (120). A positive skinprick test to povidone-iodine and povidone extract and the presence of serum-specific IgE to povidone demonstrate a Type I IgE-mediated hypersensitivity. Allergic contact dermatitis, a Type IV cell-mediated hypersensitivity reaction, is more common with povidone-iodine. Patch testing to diagnose this type of reaction is best done with dried 10% povidone-iodine solution, because long exposure to povidone-iodine in the aqueous state may yield a false-positive result due to direct skin irritation (121).

Iodinated Contrast Material. Contrast drugs do not undergo substantial metabolism and contain small amounts of free iodine. Whereas povidone-iodine contains a loose complex of iodine and surfactant (polyvinylpyrrolidone), iodinated contrast drugs contain covalently bound iodine (122). Patients with adverse reactions to povidone-iodine are not at risk for adverse reactions to iodinated contrast dyes. Reactions to contrast drugs have been attributed to ionic side

groups, osmolality, protein binding, partition coefficients, and pi electron density. Most reactions to nonionic contrast drugs are minor events such as flushing or skin rashes, appear in a significant number of patients, and are preventable by premedication with antihistamines and steroids (123). These reactions are due to nonspecific histamine release and are not immune in origin.

Anaphylactoid reactions to hyperosmolar, ionic, iodinated contrast material (ICM) are rare but are more common than those to nonionic material. These reactions account for 2.4%–3.1% of all adverse reactions, are more frequent in patients who have experienced a previous reaction, and are not prevented by premedication with steroids (124,125). Other important risk factors include asthma, atopy, cardiac disease, and β-blocker use (126). Female sex and age increase the severity of anaphylactoid reactions to ICM (126). Specific IgE (IgE RIA) against ICM has been detected in a few patients with positive skin tests (127).

Chlorhexidine. Chlorhexidine is widely used all over the world as a skin disinfectant before surgery or invasive procedures and in the general population in mouthwash or for disinfecting minor scratches (128). Therefore, patients may become sensitized before a surgical procedure. A report in the literature describes four patients with a history of minor rashes or faints in connection with previous chlorhexidine exposure who developed severe hypotension requiring epinephrine after subsequent exposure (128,129). Skin testing (prick test with 0.5% or intradermal test with 0.0002% chlorhexidine) was positive for chlorhexidine, demonstrating a Type I IgE-mediated reaction (129).

Latex. NRL is the milky, white fluid derived from the *Hevea brasiliensis* tree and is a component of most sterile and nonsterile gloves used in the perioperative period. NRL is often contained in other operating room products, including tourniquets, face masks, Ambu bags, and Foley catheters. The use of universal precautions, implemented by the US FDA in the 1980s in response to the human immunodeficiency virus, led to a dramatic increase in the use of latex gloves. The high demand for latex gloves led to a decrease in manufacturing time, which in turn led to an increased protein content in gloves. This led to a dramatic increase in the incidence of latex anaphylaxis, a Type I IgE-mediated reaction. It is beyond the scope of this article to provide a complete review of latex allergy, because other publications have done so (130).

It has been reported that close to 20% of cases of intraoperative anaphylaxis are due to latex, and the incidence of cases of anaphylaxis due to latex has been increasing in the past few years (6,16). However, one report suggests that the incidence of intraoperative anaphylaxis cases due to latex may be decreasing (12.1%), in part because of an increased awareness of the problem and the avoidance of latex gloves (5). High-risk groups include health-care workers or other workers with occupational exposure; patients with multiple surgical procedures, including those with spina bifida; atopic individuals; and those with a history of fruit or food allergies (37,130). Common fruits or foods that cross-react with latex include mango, kiwi, chestnut, avocado, passion fruit, and banana. Latex exposure is more likely with parenteral or mucous membrane exposure but can also occur with cutaneous contact or via latex aeroallergens. In a study of anesthesiologists exposed to NRL, 12.5% presented with positive latex allergen-specific IgE antibody levels (Pharmacia-Upjohn CAP system) or skinprick test (nonammoniated NRL reagent pending approval by the FDA), and they had a prevalence of contact dermatitis of 24% (131). Although latex sensitization (asymptomatic latex allergy) was present in 12.5% of anesthesiologists, latex allergy with clinical symptoms was present in only 2.4% of anesthesiologists (131).

No standardized antigens for skin testing are currently available in the United States, but these are available in Europe and are considered the gold standard test. Latex-specific IgE can be detected in the patient's serum by RAST and the enzyme-allergosorbent test (37,130). Avoidance is the only effective treatment at the present time and consists of latex-free gloves and operating room equipment (132,133). It has also been recommended to perform surgical procedures in latex-allergic patients as the first case of the day to decrease the levels of latex aeroallergens (6). Two reports describe subcutaneous desensitization to latex, but some of these patients developed serious anaphylactic reactions (42,43). More recently, there have been reports of latex allergy desensitization by a repeated contact exposure protocol (44) or by rush (4-day) sublingual desensitization (45). None of these patients developed any signs of latex anaphylaxis.

Colloids. Colloids are plasma expanders used to restore intravascular fluid volume and for distension and irrigation during gynecologic endoscopic procedures (dextran 70). Albumin, dextran, hetastarch, and gelatin are colloids often used in the operating room. The incidence of allergic reactions to colloids seems to be increasing. Whereas earlier reports from the 1980s described an incidence of 0.03% for dextran and hetastarch (134,135), a French study from 1994 (136) demonstrated an overall frequency of 0.22%. Gelatins (0.34%) and dextrans (0.27%) were more likely to cause an allergic reaction than albumin (0.1%) or hetastarch (0.06%) (136). Individuals with prior drug allergies were three times more likely to develop anaphylaxis, and males were more likely than females to develop an allergic reaction (136). Egg allergy does not appear to be a contraindication to the use of albumin, because the principal egg protein, ovalbumin (45 kd), is different from human serum albumin (67 kd) (137).

A report from France demonstrated that 2.9% of intraoperative anaphylaxis cases were due to colloids (5).

IgE-mediated anaphylaxis has been proven by demonstrating IgE antibodies and positive intradermal tests against gelatins (136). Increased circulating IgG dextran-reactive antibodies are found in most adults with dextran anaphylaxis, and ELISA is used for detecting hetastarch- and dextran-reactive antibodies (IgG and IgM) in human sera (138). Hetastarch appears to be the safest colloid, because the incidence of IgG antibodies against hetastarch is very rare in the general population (139,140). There is no known cross-reactivity between the different colloids, so a particular allergy to one should not preclude the use of a different colloid.

Isosulfan Blue Dye. Isosulfan blue, a rosaniline dye of the triphenylmethane type, is the 2,5-disulfonated isomer of patent blue dye and is the only dye of its type approved for lymphatic visualization by the FDA (141). Intraoperative lymphatic mapping and sentinel lymph node biopsy, often used for breast cancer and melanoma, are made possible with intradermal or intraparenchymal 1% isosulfan blue dye, which traces the lymphatic drainage of the cancer for the detection of occult nodal metastases. The drug circulates through the venous system after lymphatic uptake, and it is common for some patients to turn blue temporarily or to have a transient decrease in the oxygen saturation. Allergic reactions to isosulfan blue dye were first reported in 1985 (142) but are more common today because of the increased use of this dye for lymphatic mapping. The incidence of allergic reaction ranges from 1% to 2% (143,144), and severe anaphylactic reactions requiring vigorous resuscitation have been reported 15–30 min after injection of isosulfan blue (143).

Isosulfan blue dye anaphylaxis is an IgE-mediated event, as confirmed by positive skin tests in patients with an episode of intraoperative anaphylaxis after the injection of the dye (144). Allergic reaction to isosulfan blue is mediated by histamine release, and intradermal testing with 0.02 mL of 1% isosulfan blue dye (from 1:10,000 to 1:100 dilutions) produces a pruritic wheal and flare response (144,145). Undiluted prick tests are also positive in cases of anaphylaxis to isosulfan blue (144). It has been recommended to avoid this dye in the future after an episode of anaphylaxis or to use pretreatment if no alternative is available (145). Further studies are recommended to evaluate the effectiveness of pretreatment with histamine 1 and histamine 2 blockers and corticosteroids in patients with a prior episode of anaphylaxis due to isosulfan blue dye. The decrease in the oxygen saturation after the use of 1% isosulfan blue dye is a common finding and should not preclude its future use.

Summary

Adverse drug reactions or side effects are usually expected, are dose dependent, and occur at therapeutic doses. Anaphylactic and anaphylactoid reactions are unexpected and dose independent and can occur at the first exposure to drugs used during anesthesia. The presentation of anaphylactic and anaphylactoid reactions is clinically indistinguishable. Anaphylaxis is IgE dependent and is detected by the presence of positive *in vitro* and *in vivo* tests and the release of tryptase, a mast cell protease, during the reaction. Anaphylactoid reactions occur through a direct nonimmune-mediated release of mediators or complement activation and are IgE independent but can be associated with mast cell and/or basophil activation and increased tryptase.

Although anaphylaxis is a rare intraoperative event, most drugs used in the perioperative period can lead to anaphylaxis. Unfortunately, documentation of anaphylaxis is often lacking because the cause and effect relationship is often hard to prove and because the diagnosis is not easy to make with the patient under anesthesia. Furthermore, only a minority of patients get referred for allergy testing to confirm the offending drug. Muscle relaxants and NRL are the most common anesthetic drugs or substances that may lead to anaphylaxis. Prevention is the most important component to decrease the incidence of anaphylaxis. Documentation of anaphylaxis during anesthesia, referral to an allergist for identification of the causative drug, and appropriate labeling of the patient are essential to prevent future episodes of anaphylaxis.

References

1. Portier MM, Richet C. De l'action anaphylactique de certains venims. C R Soc Biol 1902;54:170–2.
2. Levy JH, Yegin A. Anaphylaxis: what is monitored to make a diagnosis? How is therapy monitored? Anesthesiol Clin North Am 2001;19:705–15.
3. Adkinson F, Pongracic J. Drug allergy. In: Holgate ST, Church MK, Lichtenstein LM, eds. Allergy. 2nd ed. London: Mosby, 2001:155–62.
4. Castells MC, Horan RH, Ewan PW, et al. Anaphylaxis. In: Holgate ST, Church MK, Lichtenstein LM, eds. Allergy. 2nd ed. London: Mosby, 2001:163–73.
5. Laxenaire MC, Mertes PM, Benabes B, et al. Anaphylaxis during anaesthesia: results of a two-year survey in France. Br J Anaesth 2001;87:549–58.
6. Vervloet D, Magnan A, Birnbaum J, et al. Allergic emergencies seen in surgical suites. Clin Rev Allergy Immunol 1999;17:459–67.
7. Laxenaire MC. Epidemiologie des reactions anaphylactoides peranesthesiques: quatrieme enquete multicentrique (juillet 1994-decembre 1996). Ann Fr Anesth Reanim 1999;18:796–809.
8. Fisher MM, Baldo BA. The incidence and clinical features of anaphylactic reactions during anesthesia in Australia. Ann Fr Anesth Reanim 1993;12:97–104.
9. Fasting S, Gisvold SE. Serious intraoperative problems: a five-year review of 83,844 anesthetics. Can J Anaesth 2002;49:545–53.

10. Lieberman P. Anaphylactic reactions during surgical and medical procedures. J Allergy Clin Immunol 2002;110:S64–9.
11. Jacobsen J, Lindekaer AL, Ostergaard HT, et al. Management of anaphylactic shock evaluated using a full-scale anaesthesia simulator. Acta Anaesthesiol Scand 2001;45:315–9.
12. Levy JH. Allergic reactions during anesthesia. J Clin Anesth 1988;1:39–46.
13. Moneret-Vautrin DA, Laxenaire MC. The risk of allergy related to general anaesthesia. Clin Exp Allergy 1993;23:629–33.
14. Schatz M, Fung DL. Anaphylactic and anaphylactoid reactions due to anesthetic agents. Clin Rev Allergy 1986;4:215–27.
15. Mertes PM, Laxenaire MC. Allergic reactions occurring during anaesthesia. Eur J Anaesthesiol 2002;19:240–62.
16. Vervloet D, Pradal M, Castelain M. Drug allergy. 2nd ed. Uppsala, Sweden: Pharmacia & Upjohn, 1999.
17. Koppert W, Blunk JA, Petersen LJ, et al. Different patterns of mast cell activation by muscle relaxants in human skin. Anesthesiology 2001;95:659–67.
18. Schwartz LB, Bradford TR, Rouse C, et al. Development of a new, more sensitive immunoassay for human tryptase: use in systemic anaphylaxis. J Clin Immunol 1994;14:190–204.
19. Castells MC, Irani A-M, Schwartz LB. Evaluation of human peripheral blood leukocytes for mast cell tryptase. J Immunol 1987;138:2184–9.
20. Schwartz LB, Irani A-M, Roller K, et al. Quantitation of histamine, tryptase, and chymase in dispersed human T and TC mast cells. J Immunol 1987;138:2611–5.
21. Vinuya RZ, Simon MR, Schwartz LB. Elevated serum tryptase levels in a patient with protracted anaphylaxis. Ann Allergy 1994;73:232–4.
22. Veien M, Szlam F, Holden JT, et al. Mechanisms of nonimmunological histamine and tryptase release from human cutaneous mast cells. Anesthesiology 2000;92:1074–81.
23. Fisher MM, Baldo BA. Mast cell tryptase in anaesthetic anaphylactoid reactions. Br J Anaesth 1998;80:26–9.
24. Laroche D, Vergnaud MC, Sillard B, et al. Biochemical markers of anaphylactoid reactions to drugs: comparison of plasma histamine and tryptase. Anesthesiology 1991;75:945–9.
25. Crockard AD, Ennis M. Basophil histamine release tests in the diagnosis of allergy and asthma. Clin Exp Allergy 2001;31:345–50.
26. Porri F, Lemiere C, Birnbaum J, et al. Prevalence of muscle relaxant sensitivity in a general population: implications for a preoperative screening. Clin Exp Allergy 1999;29:72–5.
27. Porri F, Pradal M, Rud C, et al. Is systematic preoperative screening for muscle relaxant and latex allergy advisable? Allergy 1995;50:374–7.
28. Wasserfallen JB, Frey PC. Long term evaluation of usefulness of skin and incremental challenge tests in patients with history of adverse reaction to local anesthetics. Allergy 1995;50:162–5.
29. Lee JM, Greenes DS. Biphasic anaphylactic reactions in pediatrics. Pediatrics 2000;106:762–6.
30. Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. N Engl J Med 1992;327:380–4.
31. Nicklas RA, Bernstein IL, Li JT, et al. Algorithm for the treatment of acute anaphylaxis. J Allergy Clin Immunol 1998;101:S469–71.
32. Nicklas RA, Bernstein IL, Li JT, et al. Evaluation and management of patients with a history of anaphylaxis. J Allergy Clin Immunol 1998;101:S482–5.
33. Naguib M, Magboul MA. Adverse effects of neuromuscular blockers and their antagonists. Drug Saf 1998;18:99–116.
34. Chrusch C, Sharma S, Unruh H, et al. Histamine H3 receptor blockade improves cardiac function in canine anaphylaxis. Am J Respir Crit Care Med 1999;160:1142–9.
35. Endou M, Poli E, Levi R. Histamine H3 receptor signaling in the heart: possible involvement of Gi/Go proteins and N-type calcium channels. J Pharmacol Exp Ther 1994;269:221–9.
36. Laxenaire MC, Mata-Bermejo E, Moneret-Vautrin DA, et al. Life-threatening anaphylactoid reactions to propofol. Anesthesiology 1992;77:275–80.
37. Berry AJ, Katz JD, Brown RH, et al. Natural rubber latex allergy: considerations for anesthesiologists. Park Ridge, IL: American Society of Anesthesiologists, 1999:1–34.
38. Moscicki RA, Sockin SM, Corsello BF, et al. Anaphylaxis during induction of general anesthesia: subsequent evaluation and management. J Allergy Clin Immunol 1990;86:325–32.
39. Maria Y, Grosdidier R, Haberer JP, et al. Prospective preoperative survey of 300 patients using prick tests with muscle relaxants. Ann Fr Anesth Reanim 1989;8:301–5.
40. Weiss ME, Hirshman CA. Latex allergy. Can J Anaesth 1992;39:528–32.
41. Setlock MA, Cotter TP, Rosner D. Latex allergy: failure of prophylaxis to prevent a severe reaction. Anesth Analg 1993;76:650–2.
42. Pereira C, Rico P, Lourenco M, et al. Specific immunotherapy for occupational latex allergy. Allergy 1999;54:291–3.
43. Leynadier F, Herman D, Vervloet D, Andre C. Specific immunotherapy with a standardized latex extract versus placebo in allergic healthcare workers. J Allergy Clin Immunol 2000;106:585–90.
44. Patriarca G, Nucera E, Buonomo A, et al. Latex allergy desensitization by exposure protocol: five case reports. Anesth Analg 2002;94:754–8.
45. Patriarca G, Nucera E, Pollastrini E, et al. Sublingual desensitization: a new approach to latex allergy problem. Anesth Analg 2002;95:956–60.
46. Sanford JP. The technique of penicillin desensitization: how to reduce anaphylaxis risk when only penicillin will do. J Crit Illness 1992;7:791–5.
47. Borish L, Tamir R, Rosenwasser LJ. Intravenous desensitization to beta-lactam antibiotics. J Allergy Clin Immunol 1987;80:314–9.
48. Weiss ME. Drug allergy. Med Clin North Am 1992;76:857–82.
49. Soto-Aguilar MC, deShazo RD, Dawson ES. Approach to the patient with suspected local anesthetic sensitivity. Immunol Allergy Clin North Am 1998;4:851–65.
50. Baldo BA, Fisher MM. Substituted ammonium ions as allergic determinants in drug allergy. Nature 1983;306:262–6.
51. Matthey P, Wang P, Finegan BA, Donnelly M. Rocuronium anaphylaxis and multiple neuromuscular blocking drug sensitivities. Can J Anaesth 2000;47:890–3.
52. Fisher MM, Munro I. Life-threatening anaphylactoid reactions to muscle relaxants. Anesth Analg 1983;62:559–64.
53. Stellato C, De Paulis A, Cirillo R, et al. Heterogeneity of human mast cells and basophils in response to muscle relaxants. Anesthesiology 1991;74:1078–86.
54. Doenicke A, Soukup J, Hoernecke R, et al. The lack of histamine release with cisatracurium: a double-blind comparison with vecuronium. Anesth Analg 1997;84:623–8.
55. Laxenaire MC, Gastin I, Moneret-Vautrin DA, et al. Cross reactivity of rocuronium with other neuromuscular blocking agents. Eur J Anaesthesiol 1995;11:S55–64.
56. Neal SM, Manthri PR, Gadiyar V, Wildsmith JA. Histaminoid reactions associated with rocuronium. Br J Anaesth 2000;84:108–11.
57. Guttormsen AB. Allergic reactions during anaesthesia: increased attention to the problem in Denmark and Norway. Acta Anaesthesiol Scand 2001;45:1189–90.
58. Levy JH, Gottge M, Szlam F, et al. Weal and flare responses to intradermal rocuronium and cisatracurium in humans. Br J Anaesth 2000;85:844–9.
59. Rose M, Fisher M. Rocuronium: high risk for anaphylaxis? Br J Anaesth 2001;86:678–82.
60. Laake JH, Rottingen JA. Rocuronium and anaphylaxis: a statistical challenge. Acta Anaesthesiol Scand 2001;45:1196–203.
61. Gueant JL, Mata E, Monin B, et al. Evaluation of a new reactive solid phase for radioimmunoassay of serum specific IgE against muscle relaxant drugs. Allergy 1991;46:452–8.
62. Guilloux L, Ricard-Blum S, Ville G, Motin J. A new radioimmunoassay using a commercially available solid support for the detection of IgE antibodies against muscle relaxants. J Allergy Clin Immunol 1992;90:153–9.

63. Gueant J-L, Mata E, Namour F, et al. Criteria of evaluation and of interpretation of Sepharose drug IgE-RIA to anaesthetic drugs. Allergy 1999;54:17–22.
64. Fisher MM, Baldo BA. Immunoassays in the diagnosis of anaphylaxis to neuromuscular blocking drugs: the value of morphine for the detection of IgE antibodies in allergic subjects. Anaesth Intensive Care 2000;28:167–70.
65. Weiss ME, Adkinson NF, Hirshman CA. Evaluation of allergic drug reactions in the perioperative period. Anesthesiology 1989;71:483–6.
66. Harle DG, Baldo BA, Coroneos NG, et al. Anaphylaxis following administration of papaveretum: case report—implication of IgE antibodies that react with morphine and codeine and identification of an allergenic determinant. Anesthesiology 1989;71:489–94.
67. Benett MJ, Anderson LK, McMillan JC, et al. Anaphylactic reaction during anaesthesia associated with positive intradermal skin test to fentanyl. Can Anaesth Soc J 1986;33:75–8.
68. Clarke RS. Epidemiology of adverse reactions in anesthesia in the United Kingdom. Klin Wochenschr 1982;60:1003–5.
69. Harle DG, Baldo BA, Smal MA, et al. Detection of thiopentone-reactive IgE antibodies following anaphylactoid reactions during anaesthesia. Clin Allergy 1986;16:493–8.
70. Baldo BA, Fisher MM, Harle DG. Allergy to thiopentone. Clin Rev Allergy 1991;9:295–308.
71. Laxenaire MC, Gueant JL, Bermejo E, et al. Anaphylactic shock due to propofol. Lancet 1988;2:739–40.
72. De Leon-Casasola OA, Weiss A, Lema MJ. Anaphylaxis due to propofol. Anesthesiology 1992;77:384–6.
73. Laxenaire MC. Utilisation du Diprivan chez le patient allergique. Ann Fr Anesth Reanim 1994;13:498–502.
74. Lizaso Bacaicoa MTL, Acero Sainz S, Alvarez Puebla MJ, et al. Cutaneous response to Diprivan (propofol) and Intralipid in patients with leguminous and egg allergy. Rev Esp Alergol Immunol Clin 1998;13:153–7.
75. James JM, Burks AW, Roberson PK, Sampson HA. Safe administration of the measles vaccine to children allergic to eggs. N Engl J Med 1995;332:1262–6.
76. Watkins J. Etomidate, an 'immunologically safe' anaesthetic agent. Anaesthesia 1983;38(Suppl):34–8.
77. Fazackerley EJ, Martin AJ, Tolhurst-Cleaver CL, Watkins J. Anaphylactoid reaction following the use of etomidate. Anaesthesia 1988;43:953–4.
78. Karayan J, Lacoste L, Breuil K. Allergie a la ketamine. Ann Fr Anesth Reanim 1990;9:396–7.
79. Mathieu A, Goudsouzian N, Swider MT. Reaction to ketamine: anaphylactoid or anaphylactic? Br J Anaesth 1975;47:624–7.
80. Huttel MS, Schou Olesen A, Stoffersen E. Complement-mediated reactions to diazepam with Cremophor as solvent (Stesolid MR). Br J Anaesth 1980;52:77–9.
81. Fujita Y, Ishikawa H, Yokota K. Anaphylactoid reaction to midazolam. Anesth Analg 1994;79:811–2.
82. Nishiyama T, Hirasaki A, Odaka Y, et al. Midazolam for rapid sequence induction. Masui 1990;39:230–6.
83. Kimura K, Adachi M, Kubo K, Ikemoto Y. Incidence of histamine release after the administration of midazolam-ketamine in allergic patients. Fukuoka Igaku Zasshi 1999;90:448–56.
84. Clarke JB, Thomas C, Chen M, et al. Halogenated anesthetics form liver adducts and antigens that cross-react with halothane-induced antibodies. Int Arch Allergy Immunol 1995;108:24–32.
85. Martin JL, Kenna JG, Pohl LR. Antibody assays for the detection of patients sensitized to halothane. Anesth Analg 1990;70:154–9.
86. Hubbard AK, Roth TP, Gandolfi AJ, et al. Halothane hepatitis patients generate an antibody response toward a covalently bound metabolite of halothane. Anesthesiology 1988;68:791–6.
87. Njoku D, Laster MJ, Gong DH, et al. Biotransformation of halothane, enflurane, isoflurane, and desflurane to trifluoroacetylated liver proteins: association between protein acylation and hepatic injury. Anesth Analg 1997;84:173–8.
88. Gunaratnam NT, Benson J, Gandolfi AJ, et al. Suspected isoflurane hepatitis in an obese patient with a history of halothane hepatitis. Anesthesiology 1995;83:1361–4.
89. Martin JL, Plevak DJ, Flannery KD, et al. Hepatotoxicity after desflurane anesthesia. Anesthesiology 1995;83:1125–9.
90. Berghaus TM, Baron A, Geier A, et al. Hepatotoxicity following desflurane anesthesia [letter]. Hepatology 1999;29:613–4.
91. Dietrich W, Spath P, Zuhlsdorf M, et al. Anaphylactic reactions to aprotinin reexposure in cardiac surgery: relation to antiaprotinin immunoglobulin G and E antibodies. Anesthesiology 2001;95:64–71.
92. Dietrich W, Spath P, Ebell A, et al. Prevalence of anaphylactic reactions to aprotinin: analysis of two hundred forty-eight reexposures to aprotinin in heart operations. J Thorac Cardiovasc Surg 1997;113:194–201.
93. Lemm G, Zuhlsdorf M, Jegert F, et al. Detection of aprotinin specific IgG and IgE antibodies in human samples using an enzyme-linked immunosorbent assay and an immunoblot and their predictive value for anaphylaxis in aprotinin reexposure during repeated cardiac surgery. Br J Clin Pharmacol 2000;174:679–80.
94. Patterson R, DeSwarte RD, Greenberger PA, et al. Drug allergy and protocols for management of drug allergies. 2nd ed. Providence, RI: OceanSide Publications, 1995:1–27.
95. Koch P, Munssinger T, Rupp-John C, Uhl K. Delayed-type hypersensitivity skin reactions caused by subcutaneous unfractionated and low-molecular-weight heparins: tolerance of a new recombinant hirudin. J Am Acad Dermatol 2000;42:612–9.
96. Moreau A, Dompmartin A, Esnault P, et al. Delayed hypersensitivity at the injection sites of a low-molecular-weight heparin. Contact Dermatitis 1996;34:31–4.
97. Porsche R, Brenner ZR. Allergy to protamine sulfate. Heart Lung 1999;28:418–28.
98. Levy JH. Hemostatic agents and their safety. J Cardiothorac Vasc Anesth 1999;13(4 Suppl 1):6–11.
99. Nicklas RA, Bernstein IL, Li JT, et al. Protamine. J Allergy Clin Immunol 1998;101:S507–9.
100. Knape JTA, Schuller JL, De Haan P, et al. An anaphylactic reaction to protamine in a patient allergic to fish. Anesthesiology 1981;55:324–5.
101. Samuel T, Kolk AHJ, Rumke P, Van Lis MJ. Autoimmunity to sperm antigens in vasectomized men. Clin Exp Immunol 1975;21:65–74.
102. Samuel T. Antibodies reacting with salmon and human protamines in sera from infertile men and from vasectomized men and monkeys. Clin Exp Immunol 1977;30:181–7.
103. Levy JH, Schweiger IM, Zaidan JR, et al. Evaluation of patients at risk for protamine reactions. J Thorac Cardiovasc Surg 1989;98:200–4.
104. Adourian UA, Shampaine EL, Hirshman CA, et al. High-titer protamine-specific IgG antibody associated with anaphylaxis. Anesthesiology 1993;78:368–72.
105. Metz S. Prior vasectomy and anaphylaxis following protamine: no cause and effect. Anesthesiology 1993;79:617–8.
106. Lakin JD, Blocker TJ, Strong DM, Yocum MW. Anaphylaxis to protamine sulfate mediated by a complement dependent IgG antibody. J Allergy Clin Immunol 1978;61:102–7.
107. Weiss ME, Nyhan D, Peng ZK, et al. Association of protamine IgE and IgG antibodies with life-threatening reactions to intravenous protamine. N Engl J Med 1989;320:886–92.
108. Nicklas RA, Bernstein IL, Li JT, et al. Beta-lactam antibiotics. J Allergy Clin Immunol 1998;101:S498–501.
109. Salkind AR, Cuddy PG, Foxworth JW. Is this patient allergic to penicillin? An evidence-based analysis of the likelihood of penicillin allergy. JAMA 2001;285:2498–505.
110. Romano A, Mayorga C, Torres MJ, et al. Immediate allergic reactions to cephalosporins: cross-reactivity and selective responses. J Allergy Clin Immunol 2000;106:1177–83.
111. San Miguel MM, Gaig P, Bartra J, Garcia-Ortega P. Postoperative rash to ceftriaxone. Allergy 2000;55:977–9.

112. Warrington RJ, McPhillips S. Independent anaphylaxis to cefazolin without allergy to other beta-lactam antibiotics. J Allergy Clin Immunol 1996;98:460–2.
113. Anne S, Reisman RE. Risk of administering cephalosporin antibiotics to patients with histories of penicillin allergy. Ann Allergy Asthma Immunol 1995;74:167–70.
114. Kelkar PS, Li JTC. Cephalosporin allergy. N Engl J Med 2001; 345:804–9.
115. Goodman EJ, Morgan MJ, Johnson PA, et al. Cephalosporins can be given to penicillin-allergic patients who do not exhibit an anaphylactic response. J Clin Anesth 2001;13:561–4.
116. Renz CL, Laroche D, Thurn JD, et al. Tryptase levels are not increased during vancomycin-induced anaphylactoid reactions. Anesthesiology 1998;89:620–5.
117. Anne S, Middleton E Jr, Reisman RE. Vancomycin anaphylaxis and successful desensitization. Ann Allergy 1994;73:402–4.
118. Blas M, Briesacher KS, Lobato EB. Bacitracin irrigation: a cause of anaphylaxis in the operating room. Anesth Analg 2000;91: 1027–8.
119. Sprung J, Schedewie HK, Campine JP. Intraoperative anaphylactic shock after bacitracin irrigation. Anesth Analg 1990;71: 430–3.
120. Lopez Saez MP, de Barrio M, Zubeldia JM, et al. Acute IgE-mediated generalized urticaria-angioedema after topical application of povidone-iodine. Allergol Immunopathol 1998;26: 23–6.
121. Kozuka T. Patch testing to exclude allergic contact dermatitis caused by povidone-iodine. Dermatology 2002;204(Suppl 1): 96–8.
122. Hauben M. Seizures after povidone-iodine mediastinal irrigation [letter]. N Engl J Med 1993;328:355.
123. Lasser EC, Berry CC, Mishkin MM, et al. Pretreatment with corticosteroids to prevent adverse reactions to nonionic contrast media. AJR Am J Roentgenol 1994;162:523–6.
124. Laroche D, Namour F, Lefrancois C, et al. Anaphylactoid and anaphylactic reactions to iodinated contrast material. Allergy 1999;54(Suppl 58):13–6.
125. Bettmann MA, Heeren T, Greenfield A, Goudey C. Adverse events with radiographic contrast agents: results of the SCVIR contrast agent registry. Radiology 1997;203:611–20.
126. Moneret-Vautrin DA, Kanny G, Morisset M, et al. Anaphylactoid reactions and late skin reactions to iodinated contrast media: present state of the question—idea development [in French]. Rev Med Interne 2001;22:969–77.
127. Laroche D, Aimone-Gastin I, Dubois F, et al. Mechanism of severe immediate reactions to iodinated contrast material. Radiology 1998;209:183–90.
128. Garvey LH, Roed-Petersen J, Husum B. Anaphylactic reactions in anaesthetised patients: four cases of chlorhexidine allergy. Acta Anaesthesiol Scand 2001;45:1290–4.
129. Garvey LH, Roed-Petersen J, Menne T, Husum B. Danish allergy centre: preliminary results. Acta Anaesthesiol Scand 2001;45:1204–9.
130. Hepner DL, Castells MC. Latex allergy: an update. Anesth Analg 2003;96:1219–29.
131. Brown RH, Schauble JF, Hamilton RG. Prevalence of latex allergy among anesthesiologists: identification of sensitized but asymptomatic individuals. Anesthesiology 1998;89:292–9.
132. Kurup VP, Fink JN. The spectrum of immunologic sensitization in latex allergy. Allergy 2001;56:2–12.
133. Poley GE, Slater JE. Latex allergy. J Allergy Clin Immunol 2000;105(6 Pt 1):1054–62.
134. Isbister JP, Fisher MM. Adverse effects of plasma volume expanders. Anaesth Intensive Care 1980;8:145–51.
135. Porter SS, Goldberg RJ. Intraoperative allergic reaction to hydroxyethyl starch: a report of two cases. Can Anaesth Soc J 1986;33:394–8.
136. Laxenaire MC, Charpentier C, Feldman L. Anaphylactoid reactions to colloid plasma substitutes: incidence, risk factors, and mechanisms—a French multicenter prospective study [in French]. Ann Fr Anesth Reanim 1994;13:301–10.
137. Smith SA, Geha D, Alston TA. Egg allergy and blood products: you say albumen, I say albumin. . . Anesthesiology 2003;98: 1304–5.
138. Dieterich H-J, Kraft D, Sirtl C, et al. Hydroxyethyl starch antibodies in humans: incidence and clinical relevance. Anesth Analg 1998;86:1123–6.
139. Kreimeier U, Christ F, Kraft D, et al. Anaphylaxis due to hydroxyethyl starch-reactive antibodies. Lancet 1995;346: 49–50.
140. Kraft D, Sirtl C, Laubenthal H, et al. No evidence for the existence of preformed antibodies against hydroxyethyl starch in man. Eur Surg Res 1992;24:138–42.
141. Montgomery LL, Thorne AC, Van Zee KJ, et al. Isosulfan blue dye reactions during sentinel lymph node mapping for breast cancer. Anesth Analg 2001;95:385–8.
142. Longnecker SM, Guzzardo MM, Van Voris LP. Life-threatening anaphylaxis following subcutaneous administration of isosulfan blue 1%. Clin Pharm 1985;4:219–21.
143. Albo D, Wayne JD, Hunt KK, et al. Anaphylactic reactions to isosulfan blue dye during sentinel lymph node biopsy for breast cancer. Am J Surg 2001;182:393–8.
144. Laurie SA, Khan DA, Gruchalla RS, et al. Anaphylaxis to isosulfan blue. Ann Allergy Asthma Immunol 2002;88:64–6.
145. Lyew MA, Gamblin TC, Ayoub M. Systemic anaphylaxis associated with intramammary isosulfan blue injection used for sentinel node detection under general anesthesia. Anesthesiology 2000;93:1145–6.